Healthpoint

Information from the Division of Health Care Finance and Policy

CLINICAL TRIALS: PROMISE AND PROFIT

Clinical trials—research studies involving human beings—are the final step in a long, complex, and often costly process of testing potentially promising drugs or medical devices. Required by the Food and Drug Administration (FDA) before a drug or device is approved for general use, the clinical trial process was designed to provide impartial scientific evidence of effectiveness and safety. Only approximately 20% of the drugs that start the process eventually meet the FDA's approval criteria. The National Institutes of Health's clinical trials budget for FY03 is estimated to be $2.8 billion, a 31% increase from FY01,[1] and a sum that is dwarfed by spending on trials by private pharmaceutical companies. Underscoring the increasing importance of clinical research is a new state law, effective January 1, 2003, requiring Massachusetts insurers to cover patient care costs associated with cancer treatment trials. This issue of *Healthpoint* examines the burgeoning clinical trials industry and looks at how a prescription drug goes from formulation to pharmacy.

History

Federal regulation of drugs began in 1906 with passage of the Food and Drugs Act which required that drugs meet standards of strength and purity, but not necessarily effectiveness. Significant progress was made toward more comprehensive regulation in 1938 and 1962, when laws were enacted stipulating that stringent standards of safety and effectiveness be met before a prescription drug could be marketed or sold. The 1962 legislation, recognizing the advent of clinical trials, also made informed consent a prerequisite for patients participating in such trials and required that sponsors send adverse drug reaction reports to the FDA, thus increasing its consumer protection responsibility. This responsibility expanded in 1972 when the FDA began a formal review of all over-the-counter drugs. While the first recognized randomly assigned clinical trial took place in Great Britain in the 1940s to test streptomycin in tuberculosis patients, trials didn't proliferate until the 1970s. In 2002, there were approximately 80,000 trials nationwide.[2]

FDA Involvement, Institutional Review Boards, and Patient Protection

Once a new drug or treatment has been successfully tested in laboratories and in animals—it is estimated that only 5 in 5,000 compounds that enter pre-clinical testing advance to human testing[3]—its sponsor applies to the FDA for permission to begin test-

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ing in humans. Both the FDA and a local institutional review board (IRB) must approve the trial protocol and informed consent procedures before a trial may begin. IRBs are located in hospitals and research institutions, and include physicians, scientists, non-scientists, and community members.

At present, the FDA, the federal Office for Human Research Protections, and IRBs are the three main components of patient protection. However, after the death of a participant during a clinical study of gene therapy in 1999, the U.S. Department of Health and Human Services directed the Institute of Medicine (IOM) to study and recommend ways to increase patient protection. In its recently released report, the IOM suggested establishing an independent, nonpartisan advisory body to shore up the strength of the protection system, and creating universal research standards to protect participants in both publicly and privately funded clinical studies.[4]

Description of Clinical Trials

Clinical trials test drugs, treatments or devices developed to prevent, detect, diagnose, screen for, or treat a disease, or to improve care and comfort for people with a disease or condition. Generally, there are four phases of a clinical trial. At least three phases must be completed before final FDA approval; if a fourth phase is conducted, it usually occurs after approval to explore new uses, long-term safety, and effectiveness. Phase I trials primarily determine safe dosage and how best to administer a drug while measuring its side effects; they typically last several months and include 20 to 100 people. In the case of cancer clinical trials, phase I trials generally involve patients with advanced disease who have not responded to standard treatment. About 70% of drugs tested in phase I progress to the next phase. Phase II trials involve 30 to 300 people and determine if a new drug or treatment produces the desired effect. In cancer treatment, participants are considered to have "responded" if their tumors shrink significantly or their disease progresses at a slower pace than expected. Phase III trials, which involve hundreds to thousands of people, can begin if a significant proportion of phase II patients "responded." A new drug or drug combination is compared to standard therapy or a placebo by randomly assigning patients to a control group, which receives the standard therapy, or to a treatment group, which receives the new therapy. Often phase III studies are "blind" (patients do not know which treatment they are receiving) or "double-blind" (neither patients nor investigators know who got which treatment) until the data are analyzed.[5]

FDA Approval of New Drugs

After a clinical trial is completed, the sponsor submits a new drug application (NDA) to the FDA that includes the study results, the drug's composition and how it behaves in the body, as well as how it will be manufactured and packaged. Due to external pressure from pharmaceutical companies and patients, the FDA has sped up its review of these data. The Prescription Drug User Fee Act of 1992 requires those seeking approval for a drug to pay a fee with their application, enabling the FDA to hire additional staff to review applications more quickly.

The FDA has streamlined the drug application review process by creating two categories for drugs being reviewed—standard and priority. Standard drugs (usually reviewed within a year) are expected to offer minor improvements over existing drugs. Priority drugs (usually reviewed within 6 months) represent potential major advances, so more FDA resources are provided throughout the review. The FDA also may choose to approve a drug through a process called "accelerated review," designed for drugs that are expected to have significant benefits in the long-term.[6] For example, trials of a cholesterol-lowering drug do not immediately show a reduction in deaths from heart disease,

but the drug does lower cholesterol, which other research shows is likely to eventually reduce deaths from heart disease. The FDA may require post-approval studies on a drug approved in this way.

Finally, beginning in the 1970s, the FDA permitted early use of promising, but not yet approved, investigational drugs for people with life-threatening or debilitating diseases. This shortcut was first used to treat people with beta blockers who suffered from heart and lung conditions, and later allowed the widespread expedited use of AZT for AIDS patients when its effectiveness was observed in a phase II trial.[7] In such circumstances, the FDA still requires the collection and submission of data on how patients react to the investigational drug.

Patient Participation and Recruitment

For various reasons, only a small segment of the population (3-5% of adults with cancer, for example)[8] participates in clinical research studies—relatively few patients meet trial criteria, some eligible patients are hesitant to enroll, and some doctors are reluctant to refer their patients. As researchers turn their attention from acute illnesses to increasingly prevalent chronic diseases, many more participants are needed for clinical trials since the effect of drugs typically takes longer to manifest in patients with these conditions. To expand trial enrollment and improve accessibility, academic medical centers (AMCs) are developing relationships with community hospitals and physician groups.

To better understand the various effects of new drugs on specific demographic groups, in 1988 the FDA began requiring drug sponsors to report clinical trial data by age, gender, and racial subgroup. A growing number of seniors are enrolling in trials as a result of the 2000 requirement that Medicare cover routine costs of care associated with trials. While both genders are well represented in trials, there is ongoing debate about the adequacy of racial minority representation. A recent study sponsored by the Agency for Healthcare Research and Quality documented a lack of racial and ethnic diversity among patients participating in HIV clinical trials. Especially under-represented were blacks and Hispanics, who comprise 48% of those with HIV in the United States.[9]

Insurance Coverage

Legislation requiring health plans to cover patient care costs associated with clinical trials is relatively new at the state level; as of December 2001, 15 states had such mandates. Massachusetts requires all fully insured (i.e., not self-funded) plans to cover the same patient care services (such as blood and urine tests) for enrollees in a qualified cancer treatment clinical trial that they would for patients not in a trial. Plans are not responsible for costs associated with managing the research, items provided by the trial sponsor (such as the drug itself), or the cost of services performed solely to meet the needs of the trial. Since many insurers have been covering such services for cancer patients, some assert that this mandate simply formalizes existing practice.

The Clinical Trial Industry

Clinical trials are now a distinct industry due to their growing number and the ancillary businesses that have emerged to facilitate them. While the overwhelming majority of studies in the past were administered by AMCs, many functions are now performed by private, for-profit companies devoted solely to the introduction of new drugs to the market. In 1998, only 40% of industry money was directed to AMCs, half of what was directed to them in 1990. Pharmaceutical companies now hire contract research organizations (CRO) for protocol design and trial administration, and employ their own physician-scientists, pharmacists, and statisticians to conduct the studies. In turn, CROs

develop relationships with a variety of physicians to gain access to their patients, though the pharmaceutical company retains control of the trial and the dissemination of results.

Allowing entities that have a financial stake in the results to control clinical trials eliminates the historic fire wall between those who evaluate new drugs and those who stand to profit if the tested drug is approved. Physicians increasingly report pressure, censorship, and the threat of fund cutoff by companies not wanting negative trial results published.[10] In response, the International Committee of Medical Journal Editors in 2000 revised their author guidelines in an attempt to minimize the influence of private interests. However, the *New England Journal of Medicine* recently concluded that the guidelines are not being adhered to and called for re-examining the contracting process.[11]

Policy Implications

The demand for rapid approval of drugs and devices, and the time needed to ensure safety and efficacy, remain a challenge for researchers, patients, and the FDA. The responsibilities of IRBs and the Office for Human Research Protections are increasing, yet resources remain limited. Inappropriate conduct arising from conflicts of interest must be more effectively guarded against to uphold the integrity of the clinical research process.

Endnotes

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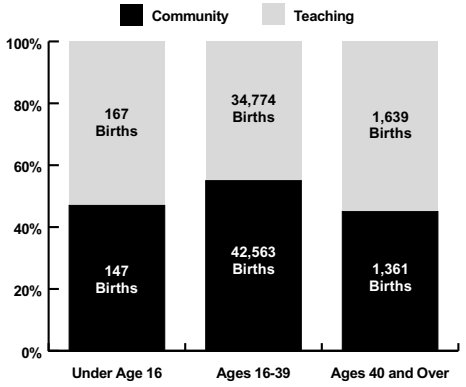
Did you know?

The Youngest and Oldest Mothers Deliver at the Same Hospitals

Both community and teaching hospitals in Massachusetts offer maternity services. In FY01, 55% of the state's 80,651 births occurred in the 38 community hospitals with maternity units. Women ages 16-39 tend to use community hospitals while women younger than age 16 and older than age 39 are more likely to deliver in teaching hospitals. Women ages 16-39 gave birth to 96% of the infants born in Massachusetts in FY01. However, the fastest growing age group of maternity patients is "ages 40 and over," which has increased 46% since 1995. By contrast, births to those younger than age 16 have decreased 39% since then.

Distribution of Massachusetts Births by Age of Mother and Hospital Type (FY01)



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